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BASIC CONCEPTS IN CARDIOLOGY

Arnold M. Katz, MD, FACC, *Guest Editor*

Influence of Altered Inotropy and Lusitropy on Ventricular Pressure-Volume Loops

ARNOLD M. KATZ, MD, FACC

Farmington, Connecticut

Each cardiac cycle can be characterized by a pressure-volume loop that graphically depicts the external work of the ventricle. The pressure-volume loop is determined to a large extent by end-diastolic and end-systolic conditions, each of which reflects the properties of the heart and circulation at these two critical times in the cardiac cycle. The pressure and volume at end-diastole and end-systole, in turn, are determined by interactions between the heart and the circulation.

End-diastolic pressure and volume reflect preload (venous return) and the lusitropic (relaxation) state of the ventricular walls, and end-systolic pressure and volume are determined by the afterload (peripheral and pulmonary resistance) and the inotropic (contractile) state of the myocardium. Alterations in inotropic and lusitropic state lead to predictable changes in the pressure-volume loop that, when combined with knowledge of preload and afterload, can facilitate understanding of the pharmacologic and pathophysiologic responses of the heart.

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The working conditions of the heart can be represented by a work diagram, or pressure-volume loop, that is constructed by simultaneously plotting the pressures and volumes in the heart. Introduced by Straub (1) in 1917 to characterize the external work of the two ventricles of the mammalian heart (Fig. 1), these curves have been used to quantify the work of the single ventricle of the turtle heart (2) and the left ventricle in an open chest canine preparation in which the right ventricle was drained by a right heart bypass (3). Although pressure-volume loops provide a useful visualization of the changing pressures and volumes during the cardiac cycle, these representations of cardiac function do not depict rates because the time scale is eliminated in their construction (Fig. 1).

The Pressure-Volume Loop

The pressure-volume loop (shown schematically in Fig. 2) begins at the end-diastolic point of the pressure-volume curve (point A) and is inscribed in a counterclockwise direction. Systole begins with isovolumic contraction, during which pressure increases at constant volume; hence, the pressure-volume loop begins with an upward deflection. During ejection, after aortic valve opening, the pressure-volume loop turns to the left. Systole ends at a point (point A') that lies on the *end-systolic pressure-volume relation*, a key determinant of ventricular function. As diastole begins and the aortic valve closes, the pressure-volume loop first falls during isovolumic relaxation. After the mitral valve opens and the filling phases begin, the pressure-volume loop rises gradually to end at a point along the *end-diastolic pressure-volume relation*. The

From the Cardiology Division, Department of Medicine, University of Connecticut, Farmington, Connecticut. This work was supported by Program Project Grant HL-33026 from the National Institutes of Health, Bethesda, Maryland.

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Address for reprints: Arnold M. Katz, MD, Division of Cardiology, University of Connecticut Health Center, Farmington, Connecticut 06032.

This article is part of a series of informal teaching reviews devoted to subjects in basic cardiology that are of particular interest because of their high potential for clinical application. The intent of the series is to help the clinician keep abreast of important advances in our understanding of the basic mechanisms underlying normal and abnormal cardiac function.

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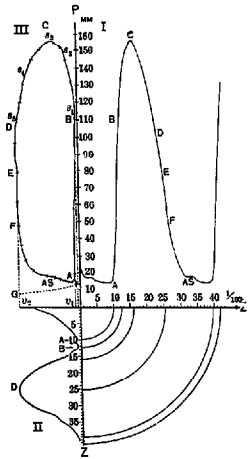

Figure 1. Method for construction of the pressure-volume loop. **I.** Relation between ventricular pressure (mm Hg, **ordinate**) and time (0.01 s, **abscissa**). **II.** Relation between ventricular volume (**abscissa**, reduced volume [v] to the left) and time (0.01 s, ordinate). The curved lines are drawn to show the identity of the two time scales that are plotted at right angles to each other. **III.** The pressure-volume loop constructed from the pressure (**ordinate**) and volume (**abscissa**) data in I and II. Note that time has been eliminated. **Capital letters** on the diagrams define data at corresponding times. AS = atrial systole. Modified from Straub (1).

latter, like the end-systolic pressure-volume relation, is an important determinant of ventricular performance.

Although this representation of the cardiac cycle provides a valuable means by which to analyze the determinants of ventricular function in humans (4–6), the effects and interplay of altered myocardial systolic and diastolic function on the pressure-volume loop have not been systematically explored. The present article, therefore, provides a theoretical analysis of altered contractile (inotropic) and relaxation (lusitropic) states on these curves.

Constraints on the Pressure-Volume Loop: End-Diastolic and End-Systolic Pressure-Volume Relations

The pressure-volume loop can be viewed as being inscribed between two points, one at end-diastole (point A, Fig. 2) and the other at end-systole (point A′, Fig. 2). Each of these points lies along a line that defines an important characteristic of ventricular performance: the end-diastolic and end-systolic pressure-volume relations, which are determined by the lusitropic and inotropic properties of the ventricle (discussion to follow). Although the end-diastolic and end-systolic pressure-volume relations reflect the properties of the ventricular myocardium, the points on these lines that constrain the pressure-volume loop are determined by the interactions between the muscular walls of the ventricle and the systemic and pulmonary circulations (Table 1).

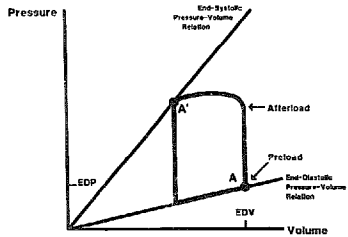

Figure 2. Schematic pressure-volume loop showing its constraint between the end-diastolic pressure-volume relation (**lower line**) and the end-systolic pressure-volume relation (**upper line**). Systole begins at the end-diastolic point (A) and ends at the end-systolic point (A′). The ventricle encounters its afterload when the aortic valve opens, so that the end-systolic point reflects both contractility and afterload. After isovolumic relaxation the ventricle begins to fill, and the preload is initially encountered when the mitral valve opens; the preload of the ventricle is defined by the pressure and volume at end-diastole. For simplicity, the ventricle is shown to fill along the end-diastolic pressure-volume curve; however, complete relaxation often does not occur until well after the onset of filling, especially in diseased hearts. EDP = end-diastolic pressure; EDV = end-diastolic volume.

End-diastolic pressure and volume (Table 1). Discovery of the role of end-diastolic pressure and volume in determining

Table 1. Determinants of the Work of the Heart

Diastolic determinants
(interplay between *preload* and *lusitropic* [relaxation] properties)
Preload (circulatory): venous return
Lusitropic state (myocardial): end-diastolic pressure-volume relation
Systolic determinants
(interplay between *afterload* and *inotropic* [contractile] properties)
Afterload (circulatory): systemic and pulmonary vascular impedance
Inotropic state (myocardial): end-systolic pressure-volume relation
Heart rate

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the work of the heart (7,8) is one of the historic cornerstones of cardiovascular physiology. The end-diastolic pressure and volume that begin the pressure-volume loop (point A, Fig. 2) are determined by an interplay between the diastolic properties of the ventricle and venous return. The former, which can be expressed as the end-diastolic pressure-volume relation of the ventricle, are a manifestation of the intrinsic *relaxation* (*lusitropic*) properties of the myocardium.

The diastolic properties of the ventricle are readily modified by drugs and disease (9,10). A positive lusitropic intervention enhances filling and so shifts the end-diastolic pressure-volume relation downward and to the right, thereby increasing ventricular filling at the same time that diastolic pressures are reduced. Conversely, a negative lusitropic intervention would shift this relation upward and to the left, thereby increasing filling pressure while reducing the size of the ventricle.

The ventricular pressure and volume that begin the pressure-volume loop are also determined by venous return, the preload that fills the ventricle. An increase in preload moves the end-diastolic point to the right and upward along the end-diastolic pressure-volume relation, and decreased venous return reduces both end-diastolic pressure and end-diastolic volume. Thus, for any given beat at constant lusitropic state, the origin of the pressure-volume loop shifts along the end-diastolic pressure-volume relation to a specific end-diastolic point that is determined by the venous return.

End-systolic pressure and volume (Table 1). The state of the ventricle at end-diastole is, of course, only one of the determinants of the pressure-volume loop. Thus, ventricular performance is also influenced by the interplay between the *contractile* (*inotropic*) state of the ventricle and *afterload*, the impedance of the arterial circulation against which the ventricle ejects its stroke volume (11). This interplay determines the end-systolic point of the pressure-volume loop (point A', Fig. 2).

The importance of changing myocardial contractility was largely overlooked until shortly after World War II because early physiologists had focused on the role of end-diastolic volume in determining cardiac function (the Frank-Starling relation, or Starling's law of the heart) (12). It was not until the mid-1950s that it came to be understood that "the regulation of the heart-beat by end-diastolic volume is but one of a number of mechanisms by which the heart's performance is adjusted to the varying physiological states of the organism" (13). Sarnoff (14), who provided an elegant demonstration of the dual control of cardiac performance by the Frank-Starling relation and myocardial contractility, clearly showed that the work of the heart depended on an interplay between end-diastolic pressure and volume *and* the contractile state of the ventricle. His concept of a "family of Starling curves" integrated the role of contractility and Starling's law of the heart as determinants of cardiac performance. One point made in the present article is that a similar "family of filling curves" also influences the work of the heart.

The end-systolic pressure-volume relation is now widely accepted as providing an excellent index of the contractile (inotropic) state of the myocardium (15). Thus, a positive inotropic intervention shifts this relation upward and to the left, thereby increasing the work that can be performed in a cardiac cycle that begins from any end-diastolic pressure and volume. Conversely, a negative inotropic intervention shifts the end-systolic pressure-volume relation downward and to the right, and so reduces the ability of the ventricle to do work.

Impedance to ejection, or afterload, determines the manner by which the mechanical energy generated by the actomyosin interactions in the ventricular walls is converted to the external work that pumps blood through the body. Most obviously, afterload is a major determinant of the pressure at which isovolumic contraction ends and ejection begins. Under conditions of constant contractility, increased afterload reduces ejection and increases pressure; conversely, when afterload decreases, a larger volume is ejected at lower pressure. In addition to influencing ejection pressure and the ability of the ventricle to empty, afterload has an important influence on cardiac efficiency in that "pressure work" is energetically more costly than "volume work" (16–18).

Interplay Between Diastolic and Systolic Determinants of the Pressure-Volume Loop

Up to this point, our discussion has considered the determinants of two key points on the pressure-volume loop: *preload* and *lusitropic state*, which together set the end-diastolic point (point A, Fig. 2), and *afterload* and *inotropic state*, which determine the end-systolic point (point A', Fig. 2). Although each of these points can be regarded as an independent determinant of the work of the heart and so of the pressure-volume loop, this is an oversimplification. Because blood flows in a circle, stroke volume, a systolic variable, also contributes to venous return and so influences end-diastolic volume. Similarly, diastolic variables influence systolic function; for example, end-diastolic volume is among the major determinants of systolic function. Conversely, end-systolic volume, the blood remaining within the ventricle after ejection, contributes to end-diastolic volume and so is a determinant of diastolic function. Thus, although it is convenient to consider systolic and diastolic function separately in analyzing the pressure-volume loop, these variables are clearly interdependent.

Effects of Alterations in Inotropic and Lusitropic State

The interplay between inotropic and lusitropic changes in determining the filling and emptying of the ventricle is

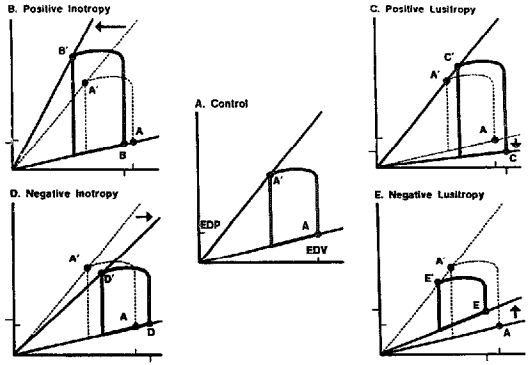

Figure 3. Schematic pressure-volume loops showing responses to positive inotropic (B), positive lusitropic (C), negative inotropic (D) and negative lusitropic (E) interventions. All examples assume a constant stroke volume. **Panel A,** Control pressure-volume loop as shown in Figure 2. This loop appears as the dashed line in panels B to E. **Panel B,** A positive inotropic intervention shifts the end-systolic pressure-volume relation upward and to the left. As stroke volume remains constant, the pressure-volume loop shifts to the left to a lower volume on the control end-diastolic pressure-volume relation (point B). **Panel C,** A positive lusitropic intervention alters the end-diastolic pressure-volume relation so that the pressure-volume loop begins at lower end-diastolic pressure and higher end-diastolic volume (point C). At constant stroke volume, the higher end-diastolic volume would cause the pressure-volume loop to end at a higher point along the control end-systolic pressure-volume relation (point C') allowing the work of the ventricle to increase at the same time that it dilates at the lower filling pressures. **Panel D,** A negative inotropic intervention shifts the end-systolic pressure-volume relation downward and to the right. With stroke volume constant, the heart dilates to new points on the depressed end-systolic pressure-volume relation (point D') and control end-systolic pressure-volume relation (point D). **Panel E,** A negative lusitropic intervention alters the end-diastolic pressure-volume relation so that the pressure-volume loop begins at higher end-diastolic pressure and lower end-diastolic volume. Contraction would begin at point E on the elevated end-diastolic pressure-volume relation. At constant stroke volume, the heart would empty to a new point (point E') on the control end-systolic pressure-volume relation. This would cause the smaller heart to reach a new steady state at a lower end-diastolic volume but a higher end-diastolic pressure. Abbreviations as in Figure 2.

complex, and difficulties in evaluating these myocardial factors in a clinical setting are compounded by concomitant changes in preload and afterload. For simplicity in the following analyses, it is assumed that there are no reflex or humorally mediated changes in preload or afterload and that neither heart rate nor cardiac output is affected by the inotropic and lusitropic interventions; thus, stroke volume remains constant in these analyses. These analyses of the effects of altered inotropic and lusitropic state on the pressure-volume loop use as a reference the control loop depicted in Figure 2, which is reproduced in the center of Figure 3.

A positive inotropic intervention (Fig. 3B). By increasing the ability of the heart to do work at any given end-diastolic pressure and volume, such an intervention causes the end-systolic pressure-volume relation to shift upward and to the left. As time is not shown on the pressure-volume loop, the effect of the positive inotropic intervention to increase the rate of pressure rise during isovolumic contraction (positive dP/dt) cannot be shown, even though this aspect of the increased contractility increases kinetic work.

Because a pure inotropic intervention does not alter diastolic properties of the ventricle, the origin of the pressure-volume loop (point B in Fig. 3B) remains on the control end-diastolic pressure-volume relation. In this example, in which stroke volume also remains constant, the ability of the inotropic intervention to shift the end-systolic point of the pressure-volume loop upward and to the left (point B' in Fig. 3B) increases ejection pressure at the same time that end-systolic volume is reduced. Because of the constant venous return, the end-diastolic point on the pressure-volume loop also shifts to the left to lower pressure and volume. As the same stroke volume is ejected from a smaller end-diastolic volume, the positive inotropic intervention has increased ejection fraction.

A positive lusitropic intervention (Fig. 3C). An increase in contractility causes the end-diastolic pressure-volume rela-

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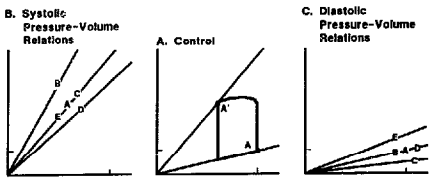

Figure 4. Changes in the intercepts of the pressure-volume loops shown in Figure 3 with the control pressure-volume loop (**A**), end-systolic (**B**) and end-diastolic (**C**) pressure-volume relations. Lettered points are taken from Figure 3, which contains the pressure-volume loops whose intercepts are summarized in this figure. Primary shifts are represented by points B and D in **B** and points E and C in **C**. Secondary shifts move along control curves: E and C in **B** and B and D in **C**.

tion to shift downward and to the right. As in the case of an inotropic intervention, such important physiologic effects on ventricular function as accelerated pressure decrease during isovolumic contraction (negative dP/dt) and increased filling rate do not alter the pressure-volume loop. In the first beat under the influence of the lusitropic intervention, end-diastolic pressure decreases and end-diastolic volume increases on the new end-diastolic pressure-volume relation (point C in Fig. 3C). Because this model allows no change in stroke volume, end-systolic volume also increases along the control end-systolic pressure-volume relation. When the new steady state is reached, the rightward shift of the pressure-volume loop causes end-diastolic volume to increase at the same time that end-diastolic pressure decreases (point C' in Fig. 3C). The ejection of a constant stroke volume from a higher end-diastolic volume reduces ejection fraction.

A negative inotropic intervention (Fig. 3D). Such an intervention shifts the end-systolic pressure-volume relation to the right and downward. The reduced ability of the ventricle to eject its end-diastolic volume causes end-systolic volume to increase (point D' in Fig. 3D). As venous return and heart rate do not change in this example, the Frank-Starling relation causes end-diastolic pressure and volume to increase along the control end-diastolic pressure-volume relation (point D in Fig. 3D) so that the heart dilates. Ejection fraction is reduced as the same stroke volume is ejected from a higher end-diastolic volume.

The constant stroke volume chosen for this example translates the reduced work of the heart caused by the negative inotropic intervention into a decrease in ejection pressure. This oversimplification is not realistic because a variety of circulatory adjustments, notably vasoconstriction, tend to maintain pressure at the expense of stroke volume (19,20).

A negative lusitropic intervention (Fig. 3E). Interventions that impair relaxation shift the end-diastolic pressure-volume relation upward and to the left. In this example, in which contractility and stroke volume are constant, filling pressure increases at a reduced end-diastolic volume (point E, Fig. 3E). The resulting shift in the pressure-volume loop to the left decreases heart size but, although filling pressure is higher, the work of the smaller ventricle (the area within the pressure-volume loop) is decreased. Because a constant stroke volume is ejected by the smaller ventricle, the end-systolic point moves down the control end-systolic pressure-volume relation to a lesser volume. As the same stroke volume is ejected by a smaller ventricle, the impaired ability of the heart to relax increases ejection fraction.

Impaired filling of the ventricle decreases end-systolic pressure and volume and is mandated by the constant stroke volume assumed in this example. This response, however, is not physiologic because these constraints do not allow for such circulatory adjustments as fluid retention and vasoconstriction, which, by increasing preload and afterload, tend to maintain blood pressure at the expense of further increases in end-diastolic pressure and a decrease in stroke volume (19,20).

Effects on ejection fraction. As mentioned in the preceding examples, changes in myocardium contractile and relaxation properties affect ejection fraction, that is, the ratio between stroke volume and end-diastolic volume. The ability of a positive inotropic intervention to increase ejection fraction (Fig. 3B) and that of a negative inotropic intervention to decrease ejection fraction (Fig. 3C) are well known and require no further comment. Less well appreciated are the effects of lusitropic interventions. Most cardiologists are aware of the tendency of the ejection fraction to be increased in patients with a markedly hypertrophied left ventricle so that a normal or high ejection fraction in patients with hypertension or aortic stenosis is not unexpected. This tendency of patients with a noncompliant ventricle to have a high ejection fraction can be predicted from the effects of a negative lusitropic intervention on the pressure-volume loop (Fig. 3E). Conversely, and initially surprising to this writer, is the prediction that a positive lusitropic intervention would decrease ejection fraction (Fig. 3C).

Primary and Secondary Shifts in End-Diastolic and End-Systolic Pressure-Volume Relations

Primary shifts. The responses of the pressure-volume loops to inotropic interventions depicted in Figure 3B and D were caused by primary changes in the end-systolic pres-

sure-volume relation, and those resulting from the lusitropic interventions illustrated in Figure 3C and E reflected primary changes in the end-diastolic pressure-volume relations. These responses are summarized in Figure 4, which shows the *primary* shifts from one end-systolic pressure-volume relation to another in the case of the inotropic effects (Fig. 4B) and, in the case of an altered lusitropic state, from one end-diastolic pressure-volume relation to another (Fig. 4C).

Secondary shifts. It can be seen from Figure 4 that these primary changes in myocardial performance state also cause *secondary* shifts along the pressure-volume relations. These secondary shifts do not arise from changes in the end-systolic or end-diastolic pressure-volume relations themselves; instead, they occur when a change in one curve moves the opposite point in the cardiac cycle along an unchanged pressure-volume relation. For example, as shown in Figure 4C, a positive inotropic intervention reduces end-diastolic volume as the result of increased ejection, even when there is no shift in the end-diastolic pressure-volume curve. Secondary changes in diastolic conditions caused by inotropic interventions are therefore able to shift end-diastolic pressure and volume along the control end-diastolic pressure-volume relation. Similarly, lusitropic interventions shift the end-diastolic point of the pressure-volume loop along the control end-systolic pressure-volume relation (Fig. 4B).

The concept of a "family of Starling curves" (14), in which an inotropic intervention shifts systolic function from one end-systolic pressure-volume curve to another, is illustrated in Figure 4B, which shows three different end-systolic pressure-volume curves. The parallel concept of a "*family of filling curves,*" in which lusitropic interventions cause the ventricle to shift from one end-diastolic pressure-volume relation to another, is shown in Figure 4C.

Combined Inotropic and Lusitropic Interventions

Interventions that alter the work of the heart often change both systolic and diastolic variables of cardiac performance. For example, agents that increase cellular levels of cyclic adenosine monophosphate enhance both inotropic and lusitropic states (21). Similarly, heart failure commonly reduces the ability of the heart to do work in a manner that impairs relaxation as well as contraction (9,10,20,22–25).

Response to combined inotropic and lusitropic effects. The effects of two commonly encountered interventions that cause simultaneous inotropic and lusitropic changes are shown in Figure 5. The first is the combination of a positive inotropic and a positive lusitropic effect (Fig. 5A) that is produced by agents, notably catecholamines, that increase cellular levels of cyclic AMP (21). The opposite combination of a negative inotropic and a negative lusitropic effect

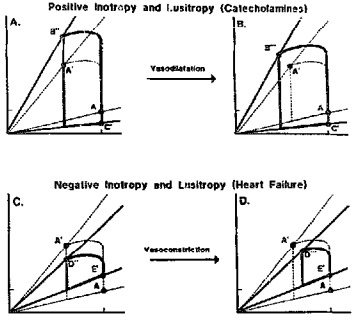

Figure 5. Schematic pressure-volume loops showing the responses to a simultaneous positive inotropic and lusitropic intervention, such as a catecholamine (**panels A and B**), and to a simultaneous negative inotropic and lusitropic intervention, such as heart failure (**panels C and D**). Panels A and C depict the response when stroke volume and heart rate are constant; panels B and D show, respectively, the effects of vasodilation and vasoconstriction. **Panel A,** Beginning at end-diastole (point A), the effect of the positive lusitropic intervention on the end-diastolic pressure-volume relation causes the pressure-volume loop to shift to a lower end-diastolic pressure-volume relation (point C'). At the same time, the upward shift in the systolic pressure-volume relation caused by the positive inotropic intervention allows the ventricle to eject to point B'''. This figure is drawn with the assumption that stroke volume does not change and that the balance between these interventions does not change end-diastolic volume. As long as peripheral resistance does not change, the result is an increased ejection pressure. **Panel B,** The pressure-volume loop in Panel A has been redrawn with the assumption that vasodilation has occurred in response to the increase in pressure. The resulting decrease in afterload moves the end-systolic point down and to the left along the new end-systolic pressure-volume relation to point B'''. Vasodilation thus allows the combined positive inotropic and lusitropic intervention to increase stroke volume. **Panel C,** Beginning at end-diastole (point A), the effect of the negative lusitropic intervention on the end-diastolic pressure-volume relation causes the pressure-volume loop to shift to a higher end-diastolic pressure-volume relation (point E'). At the same time, the downward shift in the systolic pressure-volume relation caused by the negative inotropic intervention reduces the end-systolic point to D''. This figure is drawn with the assumption that stroke volume does not change and that the balance between these interventions does not change either end-diastolic or end-systolic volume. When peripheral resistance does not change, the result is a decreased ejection pressure. **Panel D,** The pressure-volume loop in Panel C has been redrawn assuming that vasoconstriction has occurred in response to the decreased pressure. The resulting increase in afterload moves the end-systolic point up and to the right along the depressed end-systolic pressure-volume relation to point D'''. This response decreases stroke volume as well as ejection pressure.

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(Fig. 5B) commonly occurs in ischemia and congestive heart failure.

The pressure-volume loops shown in Figures 5A and B were constructed by combining the corresponding pressure-volume loops in Figure 3 assuming that, for both the catecholamine effect and the effect caused by heart failure, stroke volume and heart rate remain constant. For simplicity, it is also assumed in each case that the effects of the inotropic and lusitropic interventions on end-diastolic volume are offsetting so that end-diastolic volume remains constant. Within these constraints, the only possible expression of the combined positive inotropic and lusitropic effect is an increase in ejection pressure (Fig. 5A), while the negative inotropic and lusitropic interventions cause ejection pressure to decrease (Fig. 5B).

Response to reflex changes in arteriolar resistance. The constraints chosen for these examples, which allow no secondary changes in the pressure-volume loop other than in ejection pressure, are, of course, quite unrealistic because marked changes in cardiac function produce important reflex changes in the peripheral circulation. Thus, Figure 5 also depicts the effect on the pressure-volume loops that would result from expected reflex changes in arteriolar tone. In response to catecholamines, reflex vasodilation caused by the sharp increase in arterial pressure would shift the end-systolic point of the pressure-volume loop down and to the left along the new end-systolic pressure-volume relation (from point B″ to point B‴). The result would be an increased stroke volume and blunting of the hypertensive response to the catecholamines (Fig. 5B). Conversely, Figure 5D shows the effect of the reflex vasoconstriction commonly encountered in patients with heart failure. The increased afterload in this state shifts the end-systolic point of the pressure-volume loop along the end-systolic pressure-volume relation up and to the right (from D″ to D‴), thereby tending to maintain blood pressure at the expense of a decrease in cardiac output.

Effects of catecholamines and heart failure. The reader who has followed the reasoning on which this analysis has been based would at this point find it advantageous to use the curves in Figure 5 as a basis to complete the analysis of the effects of catecholamines and heart failure on the circulation also taking into account changes in preload. In the response to catecholamines, decreased peripheral resistance would increase cardiac output, so that the analysis shown in Figure 5B should be modified to include the expected increase in venous return. In the patient with heart failure (Fig. 5D), salt and water retention would act synergistically with the reduced ability of the heart to eject so as to increase preload. Each of these effects would modify the pressure-volume loop in a predictable manner, so that the reader is encouraged to draw additional pressure-volume loops to develop a more realistic picture of the cardiovascular response in these examples.

Clinical Implications

The "armchair" physiology presented in this article should be useful in analyzing the response of the circulation to a wide variety of physiologic, pharmacologic and pathologic interventions. In this way it should be possible to use pressure-volume loops to assess the effects of different forms of heart disease and to predict responses to the many therapeutic options now available for the treatment of the patient with cardiac disease. It is my view that the ability to predict such responses, coupled with the precise technology now available to analyze the clinical response to therapy, provides the physiologically oriented physician with a powerful means to optimize the benefits and to minimize the side effects of therapy.

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